REMARKS

The Office Action of July 28, 2004 presents the examination of claims 1-83. These claims are canceled, being replaced by the present claims 84-163. This method of amendment was chosen for its editorial simplicity.

Support for the new claims

The present claims are directed to the subject matter of the prior claims 1-83. In general, the recitations of the claims are similar to those of the original claims. The present claims are organized as a set directed to chimeric viruses, and an immunogenic composition comprising one of those viruses, and as a set of isolated polynucleotides, and methods for making the viruses by expression of one of those polynucleotides or a vector comprising one of those polynucleotides.

The new independent claim 84 recites a chimeric virus that comprises a genome or antigenome that is a chimera of HPIV3 and BPIV3 sequences in which at least one of the HN or F genes of a human PIV are present, the virus being attenuated at least 10-fold in the respiratory tract of a primate host compared to wild-type HPIV3. Claim 84 finds support in the specification at, e.g. page 11, line 21-24. The particular degree of attenuation, of at least 10-fold in the respiratory tract of a primate host, is disclosed at, e.g. Table 3 on page 86. See also page 33, at line 28 and page 65, line 29-32.

The new independent claim 85 recites that the chimeric genome or antigenome comprises a wild-type L protein and the virus is attenuated at least 10-fold in the respiratory tract of a primate host compared to wild-type HPIV3. The inclusion of a wild-type L protein is shown in the working examples, for instance as illustrated in Figure 8C in which the glycoprotein genes HN and F are interchanged between HPIV 3 and BPIV3, with retention of wild-type L protein in both instances. See also Example 1, in which only the N protein of HPIV3 is replaced by the N protein of BPIV3, and thus the L protein of the chimera is the wild-type HPIV3 L protein.

Claims 86 and 88 recite that the N gene is a BPIV3 N gene. See Example 1. Operable linkage to regulatory sequences operable in the chimeric PIV genome is described generically at, e.g. page 31, lines 5-10 and with reference to the N gene at at page 70, lines 11-14. See also Figure 1.

Claims 87 and 89 recite that the chimeric genome or antigenome comprises a human PIV3 P gene and/or L gene, or the open reading frames thereof operatively linked to operable regulatory sequences. This is described at, for instance, page 9, lines 25-28 and page 26, lines 25-28.

The incorporation of HN and/or F genes, as whole genes, or as open reading frames linked to operable regulatory sequences, is described in many places in the specification. See, e.g. page 31, lines 15-20; page 34, line 30 to page 35, line 4; Example IV beginning at page 78.

Claims 102-104 recite a number of additional point mutations that might be incorporated into the chimeric genome or antigenome. These particular mutations are described in the specification at, e.g. 39, line 24 to page 40, line 31.

Incorporation of "supernumerary genes" or open reading frames thereof is described at, e.g. page 34, line 33 to page 35, line 1. See also, page 18, lines 34 ff.; page 35, lines 34 to page 36, line 6. Use of regulatory regions together with open reading frames is contemplated as shown by description at, e.g. page 36, lines 33-34 and page 37, lines 27-28 (a "transcription unit comprising an open reading frame"). Substitution of gene start and gene end sequences is described at, e.g. page 50, lines 14-15. See also p. 52, lines 21-30. Use of the transcription regulatory sequences from the background vector is illustrated in Figure 1.

New claims 153-163 recite that the "additional virus" from which a supernumerary gene is obtained is RSV. This is described at, e.g. page 37, line 20.

The corresponding claims related to isolated polynucleotides are similarly supported.

Substance of the Interview

A personal interview with the Examiner and her Supervisor was held on July 13, 2005 and a further telephone discussion with the Examiner was held later that day. Applicants wish to thank the Examiner and her Supervisor very much for providing so much of their time to help resolve the issues in this matter.

Applicants first addressed the Collins and Klein references of record. Applicants explained that Collins (US 6,264,957) is not citable to support an obviousness rejection, being prior art only under 35 USC section 102(e) and subject to common ownership with the present application at the time the invention was made. Klein was explained as irrelevant to the present invention, being directed to producing subunit vaccines that are composed of proteins expressed in *in vitro* cultures.

Applicants presented proposed claim amendments that were considered by the Examiner and further explained how the amended claims were patentable over the Belshe reference (US 5,869,036). The Examiner or her supervisor provided some comment upon the proposed claims, such comments generally being limited to suggestions for avoiding possible rejections for lack of written description. It was acknowledged that Applicants' proposed claims, which are reflected in the claims presented in this paper and include the suggestions of the Examiner or her Supervisor, would likely be considered to distinguish the invention over Belshe.

The Examiner also agreed that claims to embodiments of chimeric viruses, immunogenic compositions comprising such viruses, isolated polynucleotides constituting the genomes of such viruses, expression vectors constituting such polynucleotides, methods for making the chimeric viruses, and methods for immunization using the viruses, would all be examined in the present application if presented.

Issues raised in the Office Action

The Office Action of July 28, 2004 presents the minor issue of claim 57 being formed of two sentences. This is moot in view of cancellation of claim 57.

Claims 1-9, 11-28, 30-32, 34-56 and 58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Belshe et al. U.S. 5,869,036. Claims 29, 33, 57 and 59-67 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Belshe in view of Collins et al. (U.S. 6,264,957) and Klein et al. (WO93/14207). Claims 1-67 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 91, 96-117, 122-129 and 141-143 of the copending application 09/083,793. Claims 1-67 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 91-93, 97-100 and 102-128 of the copending application 09/424,628. Claims 1-67 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-4, 42, 44-50, 55-61, 74, 77-79 and 81-94 of the copending application 09/733,692. Finally, claims 1-67 are provisionally rejected under 35 U.S.C. § 101 as being directed to the same subject matter as claims 1-67 of copending application no. 10/030,544.

All of the above rejections are moot in view of the substitution of the present claims 84-163 for the prior claims 1-83. Applicants submit that the above-stated rejections should not be applied against the present claims 84-163.

Rejections for double patenting

The application no. 10/030,544 has been abandoned, rendering moot the rejection under 35 U.S.C. § 101 over this application. However, Applicants have filed Continuation Applications claiming priority of the '544 application.

Applicants note the provisional nature of the rejection for statutory double patenting. Applicants submit that this rejection should be held in abeyance until at least one of the co-pending applications is allowed. Applicants note that the present claims have been amended, and amendments may be made to the copending applications. Applicants will address any statutory double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Applicants note the provisional nature of the rejections for obviousness-type double patenting. Applicants submit that these rejections should be held in abeyance until at least one of the co-pending applications is allowed. Applicants note that the present claims have been amended, and amendments may be made to the copending applications. Applicants will address any obviousness-type double patenting issues in an appropriate fashion in any particular application once one or more of the group of copending applications is allowed.

Rejection for obviousness

The present claims 84-163 should not be deemed unpatentable under 35 U.S.C. § 103(a) as obvious over Belshe '036 in view of Collins '957 and Klein '207. As explained in the interview, Collins '957 is not available to the Examiner to make a rejection grounded on 35 U.S.C. § 103(a). 35 U.S.C. § 103(c). The present application was filed after November 29, 1999 and Collins '957 was assigned to the same entity, the Government of the United States of America as represented by the Department of Health and Human Services, as the present application was to be assigned at the time the present invention was made. This is evidenced by the eventual assignment of this application to that entity recorded at reel 011182, frame 0053 on September 25, 2000. Applicants' Representative notes that all of the inventors named on this application were employees of the National Institutes of Health and had an obligation, via an employment agreement, to assign their rights in the present invention to the Government of the United States of America as represented by the Department of Health and Human Services at the

time the invention was made. Applicants will present evidence of such employment agreements at the request of the Examiner.

As was also explained in the interview, Klein '207 is not at all relevant to the present invention. Klein et al. describe making chimeric antigens, for example a chimera of a glycoprotein of a PIV with a glycoprotein of RSV, and then expressing the chimeric protein as a heterologous protein from a eukaryotic host cell in culture. See, for example, Examples 5-7, beginning at page 18 of the reference, describing expression of F_{PIV3}-F_{RSV} chimeric glycoprotein F from a baculovirus vector in Sf9 cells.

Such disclosure is not even remotely related to the present invention, in which a genome for a live, infectious, chimeric parainfluenza virus is constructed from the genomes of a bovine parainfluenza virus and a human parainfluenza virus. Other than perhaps providing description of what might be an interesting gene for an antigen to include in such a chimeric genome, Klein '207 tells one of ordinary skill in the art nothing at all about any feature of the present invention, nor anything about how to make or use the present invention.

As to the Belshe reference, Applicants have previously argued that Belshe '036 is not enabling of its disclosed embodiments and Applicants maintain their view that such is the case. However, the USPTO has made clear, in this and other applications of the Applicants, their position that concession that Belshe is not enabling of its disclosure includes an admission that the reference does not enable its claims and would therefore be invalid and that such a finding will not be made without intercession of the Board of Appeals or other higher authority than the Examining Corps.

Thus, to advance prosecution of the present application, Applicants have presented new claims that make more clear the distinctions between the present invention and what is disclosed or suggested by Belshe.

The entirety of the Belshe '036 patent relies upon extrapolation from a single kind of experiment. That is, all of Belshe's speculation comes from the result of experiments in which growth of a cp45 strain of HPIV3 at various temperatures is complemented by a plasmid expressing one or more of the NP (described as "N" in the present application), P and L protein of the wild-type HPIV3. This experiment is summarized in the attached Exhibit 1.

HPIV3 strain cp45 was known to exhibit a temperature sensitive phenotype for replication, such that, at 39.5 °C, the replication of the virus is nil (see Table 1 at col. 6). Complementation by a plasmid expressing wild-type HPIV3 L protein provides some very small degree of recovery of virus plaques at the non-permissive temperature; about 300 or so plaques were formed, in comparison with the yield of 8×10^6 seen for the wild-type HPIV3 (compare Table 3 at col. 8 with Table 1 at col. 6).

Belshe concluded that the temperature sensitive replication phenotype of the cp45 virus was due to mutations in the L protein. From this single conclusion, Belshe et al. speculate about how a recombinant virus can be constructed.

Applicants have previously argued strenuously that Belshe does not establish any kind of expectation of success in making the "hybrid" viruses that he describes or in making the present invention. However, as to the present claims, the Examiner should consider a few things about the Belshe reference.

First, the only genome described by Belshe et al. is a non-recombinant genome of the cp45 strain. Belshe et al. do not describe any sort of recombinant genome; they mention at col. 9, lines 64-66 that Example 7 "details methods for producing attenuated hybrid vaccines for target viruses...". However, Example 7 only provides citations of papers that describe the nucleic acid sequences of various viral genes. Belshe does state at the bottom of col. 8 that, "The gene sequence which encodes the surface glycoproteins of a target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result

in a hybrid virus." However, there is no further description of how this might be accomplished. At col. 9, lines 6-19, Belshe et al. describe that a hybrid virus should contain the 3' leader of cp45, NP ("N"), P[+C] and M proteins of cp45, a sequence encoding at least one surface glycoprotein of "an enveloped target virus" and "a variant protein which is different from the L protein of wild-type HPIV 3." All of the remaining disclosure of Belshe emphasizes that the L protein of any hybrid virus must be a variant from the wild-type L protein of cp45.

At the bottom of col. 6, Belshe et al. state that changes in the neuraminidase protein provide only minor decreases in replication, by less than a factor of 10, and therefore this protein is not a major factor in the attenuation of cp45. Belshe et al. also note that perhaps changes in the 3' leader sequence are "suspected in affecting the cold adaptive, temperature sensitivity and/or attenuation phenotypes of cp45." Thus, the only significant mechanism of attenuation that Belshe discloses or suggests is mutation of the L protein to a temperature sensitive phenotype by one or more point mutations.

To summarize, Belshe et al. only describe use of a cp45 genome or antigenome, having at least two of three defined point mutations in the L protein, to obtain an attenuated HPIV3 virus. The cp45 genome is a genome of a HPIV strain. Introduction of point mutations of the L protein that confers a temperature sensitive phenotype, and perhaps (though not definitively) in the 3' leader sequence, is the only mechanism of attenuation disclosed or suggested. Belshe et al. suggest that such an attenuated HPIV3 virus might be modified by substitution of its genes encoding the HN and/or F glycoproteins with the corresponding genes from a "target virus" among those listed at col. 8, lines 42-58. However, as explained above, and in painstaking detail previously, Belshe et al. provide no disclosure whatsoever about how to accomplish such substitution.

On the other hand, the present claims recite that a chimeric genome is formed by mixing genes from bovine PIV3 (BPIV) and human PIV3 (HPIV3) to obtain an attenuated chimeric virus. That is, the present invention achieves a host range attenuation phenotype. The claims

recite a threshold level of attenuation that is obtained *in vivo* and that is achieved by incorporation of glycoprotein genes or gene segments into a chimeric genome (claims 84 and 118) or despite the presence of a gene encoding wild-type L protein in the chimeric genome (claims 85 and 119). Thus, Belshe et al. do not disclose or suggest the instant invention. In fact, Belshe et al. teach away from the invention so claimed. Accordingly, all of the present claims 84-163 are both novel and unobvious over Belshe et al.

Dependent claims 86, 88, 120 and 122, and claims dependent thereon, recite incorporation of an N gene from BPIV3, a modification in no way disclosed or suggested by Belshe. In fact, Figure 1 of Belshe shows no mutation at all in the N (NP) gene, so Belshe could never have contemplated that this protein would have any effect of attenuation. Thus, Belshe et al. do not suggest incorporation of this BPIV gene into a chimeric genome. Claims 97, 98, 131 and 132, and claims dependent thereon, recite that the chimeric genome should incorporate the P gene from BPIV. Belshe et al in no way contemplate or suggest that this gene plays a role in attenuation nor do they disclose or suggest that this BPIV gene should be an element of a chimeric genome.

Additional dependent claims recite that an open reading frame of a gene to be introduced into the chimeric genome or antigenome is operably linked to regulatory sequences functional in the chimeric genome. Belshe on the other hand expressly discloses only that entire genes, i.e. the coding portions together with the regulatory portions, are taken from the "target virus". Belshe does not at all contemplate taking only the open reading frame from the target virus and incorporating it together with regulatory sequences from the background virus.

Klein '207 makes no disclosure that an infectious, chimeric PIV should incorporate a genome including glycoprotein genes (or open reading frames thereof) from one species of virus in another to obtain a host range attenuated phenotype. Neither does Klein '207 disclose or suggest that an attenuated infectious, chimeric PIV can be achieved despite the inclusion of a wild-type L protein in a chimeric genome. Thus, combining Klein '207 with Belshe '036 does

not remedy the deficiency of Belshe '036 to establish *prima facie* obviousness of the presently-claimed invention.

Klein '207 also fails to disclose or suggest incorporation of a bovine N or P gene (or open reading frame) into the genome of an infectious, chimeric PIV, and so the combination of Belshe '036 with Klein '207 does not remedy the deficiencies of Belshe '036 to establish *prima facie* obviousness of the present invention.

For all of the above-explained reasons, Applicants submit that the present claims 84-163 are both novel and unobvious over the disclosure of Belshe '036 alone and when taken together with the disclosure of Klein '207. Therefore, the present rejection of the prior claims 1-83 should not be applied to the present claims 84-163. The favorable action of allowance of the pending claims and passage of the application to issue is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

By /mjn/

Mark J. Nuell, Ph.D.
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Rd
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant